REMARKS

Claims 1-3, 7-17 and 21-31 are currently pending in the application. Claims 26-31 were withdrawn due to the Office's Restriction Requirement. Applicants reserve the right to file divisional applications directed to withdrawn subject matter. Applicants do not acquiesce to the propriety of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 USPQ.2d 1865 (US 1997).

I. 35 U.S.C. § 112 Rejections

Claims 1-3, 7-17 and 21-25 stand rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. Office Action mailed September 1, 2009 ("OA"), page 3. Applicants respectfully disagree.

The Office states that the specification is enabling for a method of sustained delivery or a method of treating a disease or condition wherein the retinoid active drug is tazarotenic acid and the ester prodrug is tazarotene. OA, page 3. Applicants agree that this subject matter is enabled. Pending claim 21 recites:

> 21. A method of sustained-delivery of an active drug to the vitreous of the eye of a mammal to treat a disease or condition affecting said mammal, wherein said disease or condition can be treated by the action of said active drug, comprising administering an effective amount of an ester prodrug of the active drug subconjunctivally wherein the active drug is tazarotenic acid and said ester prodrug is tazarotene.

Applicants believe the scope of claim 21 is commensurate in scope with that acknowledged as enabled by the Office and as such believe the rejection of claim 21 and its dependent claims on this ground is error. If this is not the case, please notify Applicants.

Applicants do not agree with the Office that the full scope of the claims is not enabled. Indeed, based on the pending specification, Applicants submit that all the *In re Wands* (858 F.2d 731 (Fed. Cir 1988)) factors are met:

(1) For quantity of experimentation, an assay as described in the specification would be performed using an ester prodrug and its active retionoid drug. For example, the specification provides that in the case of antibiotics, the disc diffusion assay can be used. Paragraph [0027]. In the case of neurotoxins, the specification provides that the mouse

potency assay can be used. Paragraph [0027]. The specification further provides that in the case where more than one assay is applicable to a disease of interest, the active retinoid need only be more than about 10 times more active than the prodrug in one assay. Paragraph [0027].

(2) For the amount of direction or guidance provided, the specification provides that prodrug carboxylic acid esters and esters of a phosphorous or sulfur-based acid are preferred. Paragraph [0024]. The specification further provides that preferred prodrugs are those consisting of an ester formed from the active drug which is a carboxylic acid or salt thereof and a C_{1-6} alcohol or phenol. Paragraph [0030]. The specification also provides that the ester group of the prodrug which is hydrolyzed to form the active drug should not be a lactone or a cyclic carboxylic acid ester and provides exemplary relevant receptor subtypes to target at Paragraph [0026].

(3) For the presence or absence of working examples, Example A provides a working example, particularly the use of the retinoic acid receptor binding assay. Thus, the specification enables the measurement of activity of a prodrug and its active drug. This example is not prophetic.

(4) For the nature of the invention, the invention as claimed herein relates to a finite number of retinoids wherein the active drug is more than about 10 times more active than its prodrug. This limitation is based on knowledge of those skilled in the art to test the activity of produgs and their active forms. As the specification provides, there are numerous methods to test retinoid prodrugs and their active forms available to those of ordinary skill in the art.

(5) For the state of the prior art, the Office states that "it is unclear when designing prodrugs whether the prodrug will have greater activity, less activity or no activity versus the active drug." OA, page 5. Applicants do not disagree that formulation and testing of ester prodrugs and their active retinoid drugs is required to practice the claimed invention. Importantly, however, one of ordinary skill is not expected to simply "envision" the structure of an ester prodrug that is less than 10 times as active as its active retinoid drug form. That is the purpose of experimentation and why experimentation is allowed within the scope of the *Wands* factors. Further, it is well within the state of the art to measure the activity of prodrugs and their active forms to determine if they meet the criteria of the pending claims.

(6) For the relative skill of those in the art, the issue is whether the active retionoid form of a particular ester prodrug – whether predicted or not – is more than about 10 times more active than its prodrug. This determination can be made based on the results of routine assays. One of ordinary skill in this art can interpret the assays described in the specification to determine whether a particular retinoid drug is more than about 10 times more active than its prodrug.

(7) For the predictability or unpredictability of the art, the kind of experimentation envisioned here is routine for development of a therapeutic retinoid. The application provides extensive guidance as to measuring activity as required by the claims.

(8) For the breadth of the claims, the claims recite a method of sustained-delivery of an active drug to a posterior part of an eye comprising administering an effective amount of an ester prodrug of the active drug subconjunctivally or periocularly wherein the active drug is a retinoid and is more than about 10 times as active as the prodrug. Accordingly, the claims do not encompass all retinoids; only those that are more than about 10 times as active as the prodrug. Applicants assert that this breadth is commensurate with the scope of subject matter enabled by the specification.

Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

II. 35 U.S.C. § 103 Rejections

Claims 1-3, 7-9, 12 and 15 stand rejected under 35 U.S.C. § 103(a) as obvious over Wilkin, J., Allergan, Inc. Avage (tararotene) cream, 0.1% Irvine California 92612, USA (2002), printed pages 1-17 (especially page 1) ("Wilkin"). OA, page 6. Applicants respectfully disagree.

To maintain a proper rejection under 35 **U**.S.C. § 103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or

suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

Here, Wilkin does not disclose all the claim limitations and beyond not suggesting that the claimed method be carried out, actually teaches away from it. As acknowledged by the Office, the composition of Wilkin is to treat wrinkles and certain skin abnormalities. OA, page 6. The Office states, however, that because "fine wrinkling will occur in the periocular or peribulbar region, ... the use of ... Tararotene around the eye ... would be obvious." OA, page 7. The Office goes on to state that, "regarding ... delivery of the active drug to the posterior part of the eye, it is understood that application of the retinoid prodrug to treat fine wrinkles in the manner of the prior art would obviously perform this function." OA, page 7.

Applicants strongly disagree with the Office's position that the use of tararotene to treat wrinkles and certain skin abnormalities topically renders obvious delivery of this compound to a posterior part of the eye (defined in the specification as including the uveal tract, vitreous, retina, choroid, optic nerve, or retinal pigmented epithelium (Paragraph [0004] and [0021]) to treat a disease or condition (non-limiting examples of which include retinal degeneration such as non-exudative or exudative age related macular degeneration (ARMD), choroidal neovascularization, diabetic retinopathy, acute macular neuroretinopathy, diabetic macular edema and uveitis. Paragraph [0021]).

Wilkin expressly teaches that the compound it describes should not come into contact with any part of the eye. The third line of Wilkin in bolded all capital letters states "**NOT FOR OPHTHALMIC ... USE.**" Wilkin, page 1. The PRECAUTIONS section of Wilkin states "For

external use only. Avoid contact with eyes.... If contact with eyes occurs, rinse thoroughly with water." Wilkin, page 5. The Information for Patients section states "(1) It is for use on the face. (2) Avoid contact with the eyes and mouth." Wilkin, page 5. Patient Information also states, "Keep [the drug] out of your eyes... If it gets in your eyes, wash them off with large amounts of cool water. Contact your doctor if irritation continues." Wilkin, page 11. Accordingly, Wilkin does not teach or suggest administration to a posterior part of the eye, much less any part, and instead, expressly teaches against such use.

Based on the foregoing, Applicants respectfully request that Office reconsider and withdraw the pending rejections of claims 1-3, 7-9, 12 and 15 under 35 U.S.C. § 103 over Wilkin.

Conclusion

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 01-0885.

Respectfully submitted,

Date: December 1, 2009

/Kenton Abel/
Kenton Abel
Registration No. 49,051

Please direct all inquiries and correspondence to:

Kenton Abel, Ph.D.
Allergan, Inc.
2525 Dupont Drive, T2-7
Irvine, California 92612

Telephone: 714 246 2842
Fax: 714 246 4249